

CHANGES IN CARDIAC OUTPUT AND TOTAL PERIPHERAL RESISTANCE DURING THE CAROTID SINUS BARORECEPTOR REFLEX IN THE PREGNANT RABBIT

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SUMMARY

1. The reflex cardiovascular effects of changes in pressure within the isolated carotid sinus have been examined in sixteen anaesthetized pregnant rabbits.

2. Comparison of the mean results at sinus pressures of 40 and 200 mm-Hg showed that heart rate fell by $32.1 \text{ beats min}^{-1}$ and arterial pressure was reduced by 48.2 mmHg. Cardiac output, measured by thermal dilution, fell by $25.7 \text{ ml. min}^{-1} \cdot \text{kg}^{-1}$ and total peripheral resistance was reduced by $0.292 \text{ mmHg. ml.}^{-1} \text{ min. kg.}$

3. The corresponding changes previously reported in a group of seventeen non-pregnant female rabbits were a similar fall in heart rate of $34.5 \text{ beats min}^{-1}$ but significantly greater reductions in arterial pressure of 69.8 mmHg and in total peripheral resistance of $0.432 \text{ mmHg. ml.}^{-1} \text{ min. kg.}$ However, the fall in cardiac output of $12.6 \text{ ml. min}^{-1} \cdot \text{kg}^{-1}$ was significantly smaller.

4. These observations show that the smaller blood pressure response of the pregnant rabbit to alterations in sinus pressure is due to a reduced change in total peripheral resistance.

INTRODUCTION

In the pregnant rabbit the change in blood pressure which can be evoked from the vascularly isolated carotid sinus is less than in the non-pregnant rabbit (Humphreys & Joels, 1974). We have recently reported on the relative contribution of changes in cardiac output and changes in total peripheral resistance to the alterations in arterial pressure when pressure is varied in the isolated carotid sinus of the non-pregnant female rabbit (Humphreys & Joels, 1977*b*), and the present paper describes a comparable study on pregnant rabbits to determine the contribution of the two

variables – cardiac output and total peripheral resistance – to the reduced blood pressure response during pregnancy. A preliminary account of the findings has been presented (Humphreys & Joels, 1977a).

METHODS

The investigation was carried out on sixteen New Zealand White rabbits with a gestational age 28 or 29 days (term is 31 days) and a mean weight of 3.88 kg. This investigation was made simultaneously with an identical one upon 17 non-pregnant female rabbits of mean weight 3.14 kg (Humphreys & Joels, 1977b), which serve as a control group for this study of the effects of pregnancy.

Anaesthesia was induced by infusion into an ear vein of a 3 % solution of pentobarbitone sodium B.P. (May and Baker Ltd.) in 0.9 % NaCl, and supplementary doses were given when necessary to maintain a steady plane of anaesthesia as gauged from the end-expiratory level of the airway CO_2 . A depth of anaesthesia just sufficient to prevent a withdrawal response to firm squeezing between the toes was the aim.

Cannulae were inserted into the trachea, a femoral artery and a femoral vein. The femoral arterial cannula was advanced into the abdominal aorta and served for the measurement of arterial blood pressure. A saline-dextrose solution (1 part of 0.9 % NaCl to 4 parts of 5 % dextrose) was infused through the femoral venous cannula at a rate of approximately $1.5 \text{ ml. kg}^{-1} \text{ hr}^{-1}$. Throughout the experiment a gentle stream of O_2 was passed over the tracheal cannula to slightly enrich the inspired air. Body temperature was maintained constant by the use of heating lamps when necessary.

Isolation of the carotid sinus. The right carotid sinus was prepared so that it could be temporarily isolated from the circulation and exposed to selected non-pulsatile pressures. The technique for vascular isolation and perfusion has been fully described elsewhere (Humphreys & Joels, 1977b). To minimize compensatory cardiovascular changes due to altered activity of baroreceptors in other regions, the opposite carotid sinus nerve was cut and both aortic nerves divided close to their junction with the superior laryngeal nerve.

Measurement of cardiac output. 0.6 ml. saline at room temperature was injected through a catheter inserted into the right external jugular vein with its tip positioned close to the entry of the superior vena cava into the right atrium. The resultant change in aortic blood temperature was registered by a thermistor bead carried at the tip of a catheter passed through a femoral artery and advanced into the thoracic aorta. A detailed account of the construction of the thermistor catheter, the calculation of cardiac output from the thermal dilution curve and the validation of the thermal dilution technique for use in these experiments has been given (Humphreys & Joels, 1977b).

Recordings. Systemic arterial pressure, carotid sinus pressure and superior vena caval pressure were measured by transducers (Consolidated Electrodynamics Type 4-327-L221). Superior vena caval pressure was obtained from a side-arm of the catheter used for the injection of saline for cardiac output determination. After amplification by carrier amplifiers (S.E. Laboratories, Type 432/1) the signals were displayed on a direct writing U.V. recorder (S.E. Laboratories, Model No. 2100). Mean arterial pressure was obtained by passing the systemic pressure signal through a simple R-C network with a time constant of 1 sec and was recorded by a separate galvanometer. Heart rate was counted from the pressure pulses. Airway CO_2 , measured by an I.R. CO_2 analyser (Hartmann & Braun, Type URAS4), and tidal

volume, measured by an integrating pneumotachograph (Godart NV), were also displayed on channels of the U.V. recorder. These respiratory measurements were used in conjunction with blood gas analyses to assist in the maintenance of a steady level of anaesthesia and also showed whether or not respiration was altered by the test procedure.

Test procedure. Non-pulsatile pressures of 40, 70, 100, 130, 160 and 200 mmHg were applied to the vascularly isolated carotid sinus in a random sequence. Cardiac output was determined about 25 sec after applying each selected pressure to the carotid sinus, by which time new steady levels of heart rate and arterial pressure had been established.

Blood gases. Arterial blood samples (0.7 ml) were withdrawn anaerobically and the pH, P_{O_2} and P_{CO_2} measured immediately at 39 °C with a Radiometer Type PHM 27b pH meter and Type PHA 927b Gas Monitor using calibrated Radiometer electrodes.

Calculation of cardiovascular variables. Total peripheral resistance was computed as the ratio of mean aortic blood pressure in mmHg to cardiac output in ml. min⁻¹. kg⁻¹. Venous pressure was ignored in this calculation since the superior vena caval pressure was at all times close to zero and in no procedure did its mean value change by more than 1–2 mmHg. Stroke volume in ml. kg⁻¹ was obtained by dividing cardiac output expressed as ml. min⁻¹. kg⁻¹, by heart rate. An index of left ventricular stroke work was given by the product of stroke volume per kg and mean aortic blood pressure. Left ventricular work was derived as the product of left ventricular stroke work per kg and heart rate.

Values. Unless otherwise stated all values are quoted as means \pm s.d.

RESULTS

Control values

In Table 1 the mean values for the sixteen pregnant rabbits of the present series are compared with the corresponding values for the seventeen non-pregnant female rabbits reported on previously (Humphreys & Joels, 1977b).

Body weight. The mean weight of the pregnant rabbits was 740 g more

TABLE 1. Comparison of control values (mean \pm s.d.) in sixteen pregnant and seventeen non-pregnant rabbits. One sinus nerve and both aortic nerves cut. The *P* values indicate the significance of the difference between the means of these readings in the pregnant and non-pregnant animals

	Pregnant (<i>n</i> = 16)	Non-pregnant (<i>n</i> = 17)	<i>P</i>
Weight (kg)	3.88 \pm 0.43	3.14 \pm 0.49	< 0.001
Rectal temperature (°C)	38.7 \pm 0.97	38.8 \pm 0.97	\approx 0.8
P_{a,CO_2} (mmHg)	32.7 \pm 5.5	37.6 \pm 4.15	< 0.02
pH	7.34 \pm 0.04	7.36 \pm 0.03	\approx 0.1
Heart rate (beats min ⁻¹)	288.4 \pm 17.0	287.0 \pm 23.5	\approx 0.9
Mean arterial pressure (mmHg)	77.7 \pm 15.3	103.5 \pm 8.87	< 0.001
Cardiac output (ml. min ⁻¹)	537.4 \pm 148.1	515.5 \pm 130.6	\approx 0.7
Cardiac output (ml. min ⁻¹ . kg ⁻¹)	138.9 \pm 31.9	161.5 \pm 41.5	\approx 0.2
Total peripheral resistance (mmHg. ml. ⁻¹ min. kg)	0.578 \pm 0.112	0.679 \pm 0.164	\approx 0.1

than that of the non-pregnant ones. The pregnant uterus accounted for 460 g of this difference. Most of the remaining difference can probably be ascribed to the greater development of the mammary glands and the fat deposits laid down in pregnancy.

Arterial blood gas tensions. Mean arterial P_{CO_2} was 4.9 mmHg lower in the pregnant animals, a difference similar to that found previously (Humphreys & Joels, 1974). Mean arterial pH was similar in the pregnant and non-pregnant groups. Arterial P_{O_2} was always in excess of 100 mmHg. However, values for P_{O_2} are not given in Table 1 since, due to enrichment of the inspired air with O_2 , arterial P_{O_2} was often above the level to which the O_2 electrode was calibrated.

Cardiovascular measurements. Table 1 also gives the values for cardiovascular measurements made after both aortic nerves and one sinus nerve had been cut and with the innervated carotid sinus exposed to pulsatile blood flow through the common carotid artery. As in our previous study (Humphreys & Joels, 1974) heart rates were almost identical in the two groups, but mean arterial blood pressure was lower in the pregnant group. Both cardiac output, expressed per kg body weight, and total peripheral resistance tended to be lower in the pregnant animals, though total cardiac output tended to be slightly greater in the pregnant rabbits.

Cardiovascular effects of changes in carotid sinus pressure

Fig. 1 shows the results of a representative experiment in which blood pressure, heart rate and cardiac output were measured, 25–30 sec after applying each of a series of non-pulsatile pressures ranging from 40 to 200 mmHg to the isolated carotid sinus of a pregnant rabbit. Also shown are the calculated values for total peripheral resistance and stroke volume. The pattern of changes as sinus pressure was increased from 40 to 200 mmHg resembles that seen in the non-pregnant rabbit. There were falls in heart rate, blood pressure, cardiac output and total peripheral resistance.

Comparison of cardiovascular effects in pregnant and non-pregnant animals

The mean responses of the sixteen pregnant rabbits of the present series and the seventeen non-pregnant female rabbits of Humphreys & Joels (1977b) are compared in Fig. 2, in which the mean values of heart rate, mean arterial pressure, cardiac output, total peripheral resistance, stroke volume and left ventricular work are shown at the different levels of pressure within the isolated carotid sinus.

The effects on heart rate were virtually identical in the two groups, but in the pregnant rabbits mean arterial pressure, cardiac output, calculated

total peripheral resistance and left ventricular work were all less at each level of sinus pressure.

In Table 2 the mean values of the various cardiovascular parameters at sinus pressures of 40 and 200 mmHg, together with the mean change in each parameter over this range of sinus pressure, are compared in the pregnant

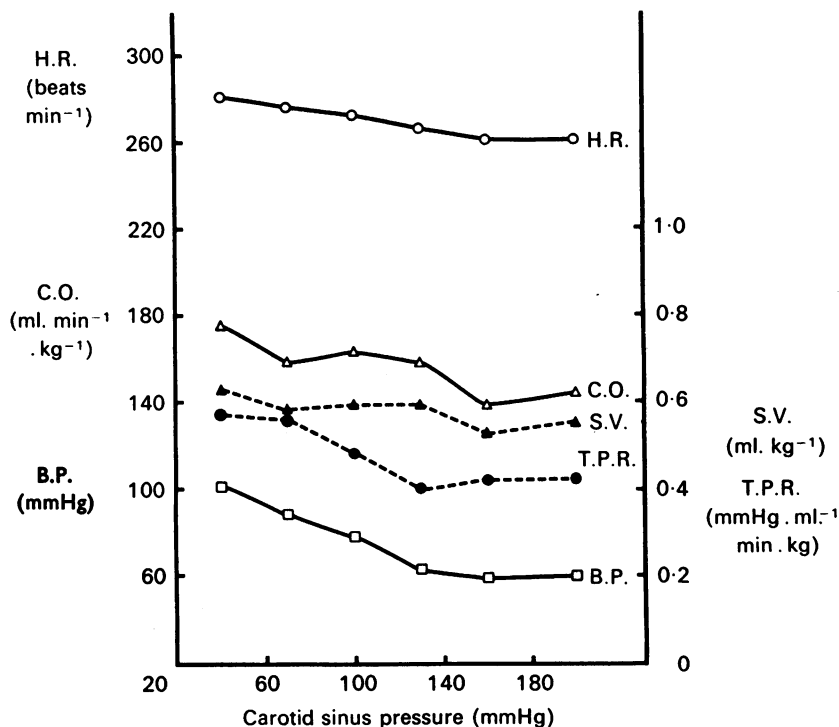


Fig. 1. Measured values for heart rate (H.R. beats min⁻¹), cardiac output (C.O. ml. min⁻¹.kg⁻¹) and arterial pressure (B.P. mmHg), and calculated values for stroke volume (S.V. ml. kg⁻¹) and total peripheral resistance (T.P.R. mmHg⁻¹. min . kg) at different levels of carotid sinus pressure in an anaesthetized pregnant rabbit.

and non-pregnant rabbits. The findings presented in this table show that the arterial pressure response to the change in sinus pressure was smaller in the pregnant rabbits, 48.2 as compared to 69.8 mmHg ($P < 0.001$). This could not have been due to the alteration in the cardiac output response, since the corresponding change in cardiac output was greater in pregnancy. The mean difference between cardiac outputs at a sinus pressure of 40 mmHg and at a sinus pressure of 200 mmHg was 25.7 ml. min⁻¹.kg⁻¹ in the pregnant rabbits, but only 12.6 ml. min⁻¹.kg⁻¹ in the non-pregnant rabbits ($P < 0.05$). These changes represent reductions in cardiac output

at the higher carotid sinus pressure of 18.2 and 7.9% in the pregnant and non-pregnant rabbits respectively. By contrast, the corresponding change in the calculated value for total peripheral resistance was less in the pregnant rabbits, $0.292 \text{ mmHg. ml.}^{-1} \text{ min. kg}$ as compared to $0.432 \text{ mmHg. ml.}^{-1} \text{ min. kg}$ ($P < 0.01$), and it is this difference which must have been responsible for the smaller blood pressure response of the pregnant animals.

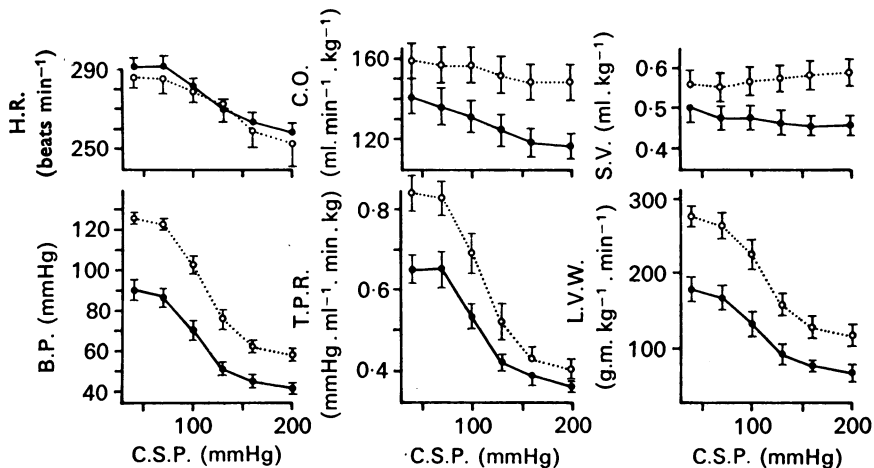


Fig. 2. Comparison of mean values (\pm S.E. of mean) of heart rate (H.R.), cardiac output (C.O.), stroke volume (S.V.), arterial pressure (B.P.), total peripheral resistance (T.P.R.) and left ventricular work (L.V.W.) at various levels of carotid sinus pressure (C.S.P.) in sixteen pregnant rabbits (continuous lines) and seventeen non-pregnant rabbits (interrupted lines).

At the lower sinus pressure stroke volume was slightly greater in the pregnant rabbits but was slightly reduced in the non-pregnant ones. Nevertheless left ventricular stroke work and left ventricular work were higher at the lower value of sinus pressure in both pregnant and non-pregnant rabbits. Moreover, in consequence of the smaller change in arterial blood pressure, the change in these parameters was less in the pregnant group.

Effects of sinus and aortic nerve section

To see whether sectioning one sinus and both aortic nerves led to an appreciable alteration in the cardiovascular variables in which we were interested, arterial pressure and cardiac output were measured in two additional pregnant rabbits immediately before cutting these nerves and 2–3 hr later. This interval was the same as that between cutting the nerves and performing the tests in the experiments described above. The values of heart rate, blood pressure, cardiac output and total peripheral resistance

TABLE 2. Comparison of values of cardiovascular parameters (mean \pm s.d.) at carotid sinus pressures of 40 and 200 mmHg (C.S.P. 40 and C.S.P. 200) in sixteen pregnant and seventeen non-pregnant rabbits. The alterations in each parameter (mean \pm s.d.) between the two levels of sinus pressure are also given (Δ C.S.P. 40-200) and the P values indicate the significance of the difference between the means of these alterations in the pregnant and non-pregnant animals

	Pregnant ($n = 16$)			Non-pregnant ($n = 17$)			P
	C.S.P. 40	C.S.P. 200	Δ C.S.P. 40-200	C.S.P. 40	C.S.P. 200	Δ C.S.P. 40-200	
Heart rate (beats min ⁻¹)	290.6 ± 16.4	258.4 ± 20.6	32.1 ± 18.3	287.4 ± 25.7	252.8 ± 35.8	34.5 ± 14.1	≈ 0.7
Arterial pressure (mmHg)	89.6 ± 18.9	41.4 ± 8.9	48.2 ± 16.5	126.3 ± 8.1	57.7 ± 11.2	69.8 ± 12.4	< 0.001
Cardiac output (ml. min ⁻¹ . kg ⁻¹)	141.3 ± 35.0	115.8 ± 25.4	25.7 ± 14.2	159.2 ± 36.7	147.8 ± 39.7	12.6 ± 19.5	< 0.05
Total peripheral resistance (mmHg.ml. ⁻¹ min.kg)	0.652 ± 0.145	0.360 ± 0.070	0.292 ± 0.117	0.836 ± 0.205	0.405 ± 0.110	0.432 ± 0.115	< 0.01
Stroke volume (ml. kg ⁻¹)	0.498 ± 0.135	0.458 ± 0.103	0.040 ± 0.051	0.559 ± 0.138	0.587 ± 0.149	-0.027 ± 0.046	< 0.001
L. ventricular stroke work (g.m.kg ⁻¹)	0.596 ± 0.190	0.260 ± 0.092	0.336 ± 0.143	0.966 ± 0.217	0.462 ± 0.148	0.507 ± 0.175	< 0.01
L. ventricular work (g.m.kg ⁻¹ .min ⁻¹)	177.1 ± 58.9	67.2 ± 24.5	109.8 ± 43.1	274.3 ± 59.3	118.2 ± 44.0	156.0 ± 46.1	< 0.01

just before cutting the nerves and 2-3 hr after they had been sectioned are shown in Table 3. There were small falls in heart rate and cardiac output in both animals and small but variable alterations in blood pressure and total peripheral resistance. These changes were of similar magnitude to those seen in non-pregnant rabbits (see Table 2 of Humphreys & Joels, 1977b) and were probably no greater than might be expected to be found between measurements made at a similar interval in an undisturbed anaesthetized animal.

TABLE 3. Heart rate (H.R.), arterial pressure (B.P.), cardiac output (C.O.) and total peripheral resistance (T.P.R.) before and 2-3 hr after cutting one sinus nerve and both aortic nerves. Each value is the mean of a pair of measurements

	Rabbit 63			Rabbit 65			Mean change (%)
	Before	After	Change (%)	Before	After	Change (%)	
H.R. (beats min ⁻¹)	293	278	-5.1	312	288	-7.6	-6.4
B.P. (mmHg)	66	67	+1.5	65	58	-10.8	-4.7
C.O. ml. min ⁻¹ . kg ⁻¹)	136	126	-7.4	89	83	-6.7	-7.1
T.P.R. (mmHg. ml ⁻¹ . min. kg)	0.487	0.527	+8.2	0.723	0.695	-3.9	+2.2

Influence of posture on the reflex baroreceptor responses

The foregoing experiments were carried out with the rabbit lying supine. To examine the possibility that in this position the weight of the gravid uterus lying on the great vessels of the posterior abdominal wall might have unduly influenced the results, the investigations were repeated in three pregnant animals with the rabbit lying on its side. This did not produce any consistent pattern of difference in the cardiovascular parameters measured at any sinus pressure. On average, when the rabbit was on its side, heart rate was 6.4 beats min⁻¹ (2.2 %) lower, blood pressure was 1.5 mmHg (2.5 %) higher and cardiac output was increased by 11.8 ml. min⁻¹. kg⁻¹ (8.6 %).

DISCUSSION

The results of this study confirm our earlier finding that in the pregnant rabbit the change in arterial pressure which can be evoked by alterations in pressure within the vascularly isolated carotid sinus is reduced, though the size of the change in heart rate is unaffected (Humphreys & Joels, 1974). In the present paper this difference is analysed by the comparison of

measurements of cardiac output and calculated values of total peripheral resistance at several levels of sinus pressure from 40 to 200 mmHg with the corresponding values in non-pregnant rabbits. This comparison has shown that although at a sinus pressure of 40 mmHg cardiac output was lower in the pregnant rabbits, when sinus pressure was increased from 40 to 200 mmHg they responded with a reduction in cardiac output which was double that in the non-pregnant rabbits (25.7 as against 12.6 ml. min⁻¹.kg⁻¹). Thus the smaller change in arterial pressure evoked from the carotid sinus in the pregnant rabbits (48.2 as against 69.8 mmHg in the non-pregnant rabbits) must be due solely to a diminished response of the total peripheral resistance. The mean change in the calculated value of the total peripheral resistance was 0.292, as against 0.432 mmHg. ml.⁻¹ min. kg in the non-pregnant animals.

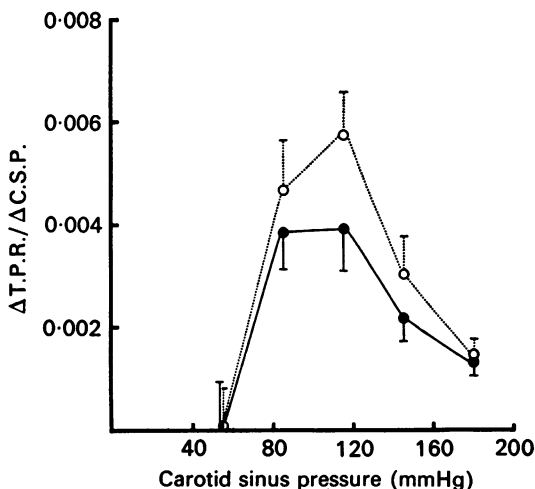


Fig. 3. Sensitivity of the baroreceptor reflex, i.e. ratio of the change in total peripheral resistance to the change in carotid sinus pressure at different levels of sinus pressure. Filled circles and continuous line, pregnant rabbits; open circles and interrupted line, non-pregnant rabbits. Vertical bars indicate S.E. of mean.

This diminished response of the peripheral resistance is unlikely to have been caused by a change in baroreceptor sensitivity since the changes in heart rate were virtually identical in the pregnant and non-pregnant animals (Fig. 2 and Table 2). A further indication that the characteristics of the carotid sinus baroreceptors are not greatly altered in pregnancy is afforded by Fig. 3. In this Figure the sensitivity of the baroreceptor reflex, i.e. the change in total peripheral resistance for a 1 mmHg change in pressure within the isolated sinus, has been calculated from the data used

in constructing Fig. 2 and the values plotted against carotid sinus pressure. The figure shows that the threshold of the baroreceptor reflex, i.e. the lowest level of sinus pressure which evokes appreciable changes in total peripheral resistance, and the levels of sinus pressure at which the sensitivity is greatest, were similar in the pregnant and non-pregnant animals.

Other potential causes for the diminished peripheral resistance response to changes in carotid sinus pressure in pregnancy include the possibility that there might be an alteration in the sensitivity of central vasomotor neurones. Though this possibility does not seem to have been examined, it merits consideration since an alteration in the sensitivity of the central respiratory neurones has been held to be responsible for the hyperventilation which occurs in pregnancy (Pernoll, Metcalfe, Kovach, Wachtel & Dunham, 1975). The lack of participation of the uterine vascular bed in reflex vascular responses (Ladner, Brinkman, Weston & Assali, 1970) may well be an important factor in the reduced response of the total peripheral resistance, as may the inhibitory effects of oestrogen and progesterone on vascular smooth muscle generally. Evidence for both these possibilities has been discussed previously at some length (Humphreys & Joels, 1974).

The measurements of cardiac output made in this investigation, which show that an alteration in the response of the cardiac output is not responsible for the reduced effect of changing carotid sinus pressure in the pregnant rabbit, are of additional interest since this is the first time that cardiac output has been measured by the same workers in a group of pregnant rabbits and a matched group of non-pregnant rabbits. Measurements made in these animals in the control situation, with the carotid region unclipped and exposed to carotid arterial pressure, showed that in the pregnant rabbits there was no significant increase in cardiac output expressed on a body weight basis; nor indeed was there a significantly greater absolute value of cardiac output (Table 1) as there is in women during pregnancy (Lees, Taylor, Scott & Kerr, 1967). On the contrary there was a strong tendency ($P \simeq 0.2$) for cardiac output expressed per kg to be less in the pregnant rabbit (138.9 as against 161.5 ml. min⁻¹. kg⁻¹). A similar pattern has been described by Duncan (1969) who measured cardiac output in pregnant rabbits at the same stage of gestation (27–29 days). She obtained a value of 105 ml. min⁻¹. kg⁻¹ and compared this with the value of 110 ml. min⁻¹. kg⁻¹ in non-pregnant rabbits reported by Neutze, Wyler & Rudolph (1968). This absence of a rise in cardiac output during pregnancy, when allowance is made for the increase in body weight, is however consistent with the relatively low values for uterine blood flow in the rabbit when these are expressed on the same unit weight basis. Duncan (1969) found mean uterine blood flow at this stage of pregnancy to be only 64 ml. min⁻¹. kg⁻¹ when measured by injection of isotope-labelled

microspheres, and a mean value of $88 \text{ ml. min}^{-1} \cdot \text{kg}^{-1}$ was reported by Cotter, Blechner & Prystowsky (1970) who used a diffusion equilibrium technique with antipyrine.

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